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The obesity paradox for middle and long-term mortality in older cancer patients: a prospective multicenter cohort study

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Short running head: The obesity paradox in older patients with cancer

Abbreviations: ADL, Activities of Daily Living; aHR, adjusted hazard ratio; BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; CRP, C-reactive protein; ELCAPA, Elderly Cancer Patients; GA, geriatric assessment; IADL, Instrumental Activities of Daily Living; mini-GDS, mini-Geriatric Depression Scale; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment; NHANES, National Health and Nutrition Examination Survey; TUG, timed up-and-go test; WHO, World Health Organization; WL, weight loss.

Clinical Trial Registry number: NCT02884375 (ClinicalTrials.gov)

Data described in the manuscript, code book, and analytic code will be made available upon request pending approval of the legal sponsor i.e APHP.

1 **Abstract**

2 **Background:** Overweight and obesity are associated with adverse health outcomes. However,
3 substantial literature suggests that they are associated with longer survival among older people.
4 This “obesity paradox” remains controversial. In the context of cancer, the association between
5 overweight/obesity and mortality is complicated by concomitant weight loss (WL). Sex-
6 differences in the relationship between BMI and survival have also been observed.

7 **Objective:** We studied whether a high body mass index (BMI) was associated with better
8 survival, and whether the association differed by sex in older patients with cancer.

9 **Design:** We studied patients aged ≥ 70 from the Elderly Cancer Patients (ELCAPA)
10 prospective open cohort (2007-2016; 10 geriatric oncology clinics, Greater Paris urban area).
11 The endpoints were 12- and 60-month mortality. We created a variable combining BMI at
12 cancer diagnosis and WL in the previous 6 months, and considered four BMI categories:
13 underweight (BMI $< 22.5 \text{ kg/m}^2$), normal weight (BMI 22.5-24.9), overweight (BMI 25-29.9),
14 obesity (BMI ≥ 30) and three WL categories: $< 5\%$ (minimal), 5- $< 10\%$ (moderate), $\geq 10\%$
15 (severe). Univariate and multivariate Cox proportional hazards analyses were conducted in
16 males and females.

17 **Results:** A total of 2071 patients were included (mean age: 81; females: 48%; underweight:
18 30%; normal weight: 23%; overweight: 33%; obesity: 14%; predominant cancer sites:
19 colorectal (18%), and breast (16%); patients with metastases: 49%). By multivariate analysis,
20 obese women with $\text{WL} < 5\%$ had a lower 60-month mortality risk than normal-weight women
21 with $\text{WL} < 5\%$ (adjusted hazard ratios: 0.56; 95% Confidence Interval: 0.37, 0.86; $p=0.012$).
22 Overweight/obese women with $\text{WL} \geq 5\%$ did not have a lower mortality risk than normal-
23 weight women. Overweight and obese men did not have a lower mortality risk, irrespective of
24 WL.

25 **Conclusion:** By taking account of prediagnosis WL, only older obese women with cancer with
26 minimal weight loss had a lower mortality risk than their counterparts with normal weight.

27

28 **Key words:** obesity paradox, body mass index, elderly, cancer, mortality, prognosis

29 **Introduction**

30 Overweight and obesity are important medical concerns worldwide, as they are associated with
31 adverse health outcomes. It has been well established that a high body mass index (BMI ≥ 25
32 kg/m^2) is associated with greater all-cause mortality (1). Among older adults aged 65 years or
33 older, literature data suggests that (i) the lowest mortality risk is found among overweight
34 people (BMI 25-29.9 kg/m^2) and (ii) the mortality risk is no greater in people with class I
35 obesity (BMI 30-34.9) than in people of normal weight (BMI 18.5-24.9) (2). In the context of
36 cancer, the association between overweight/obesity and mortality is complicated by
37 concomitant weight loss (WL) and cachexia (3). Although a high BMI is a risk factor for
38 several types of cancer (4), its prognostic value is subject to debate. The results of several
39 studies of breast cancer patients have shown that a high BMI is associated with worse survival
40 (5). In contrast, studies of many other cancer types (i.e. lung cancer (6), lymphoma (7),
41 stomach cancer (8), colon cancer (9), colorectal cancer (10) and renal cell carcinoma (11, 12))
42 either did not find an association with mortality or found an association with better survival
43 among patients with a high BMI than among patients with a normal BMI. In some studies in
44 several types of cancer, a gender-based obesity paradox has also been suggested (13). Sex
45 differences in the biology of the disease, genetic expression, hormonal effects, and in body
46 mass composition have been proposed to explain the gender-specific association between BMI
47 and mortality (14-16), suggesting that sex should be considered when evaluating the prognostic
48 value of obesity. Studies evaluating the association of BMI with survival included adults aged
49 from 19 to 100 but did not specifically analyze older cancer patients, whereas the obesity
50 paradox was originally shown in older populations. Moreover, it is known that age-related
51 physiological changes (involving an increase in fat stores and a decrease in lean body mass)
52 can alter the relationship between BMI and mortality (17).

53 Many explanations for the “obesity paradox” have been presented in the literature.
54 Methodological explanations include residual confounding, collider stratification bias,
55 detection bias and reverse causation (12, 18, 19). Indeed, patients classified in the “normal
56 weight” category at cancer diagnosis may have already lost significant weight and may thus be
57 at a greater risk of mortality than obese patients are. Other explanations concern the higher lean
58 body mass (associated with better survival) in obese patients than in normal-weight patients.
59 Lastly, for some cancer sites, putative biological and molecular mechanisms have been
60 suggested (12, 20). For example, metabolic and endocrinal changes in obese patients may
61 include tumor-suppressing effects of certain adipokines released by adipose tissue (i.e.
62 adiponectin, chemerin, and omentin), favorable fat distribution patterns, lower levels of
63 adipose tissue inflammation, and greater cardiorespiratory fitness.

64 We hypothesize that a high BMI is associated with better overall survival in older cancer
65 patients. The primary objective was to study whether a high BMI was associated with better
66 mid- and long-term survival, taking account of previous weight loss, and whether the
67 association differed by patient sex in older patients with cancer.

68

69 **Materials and Methods**

70

71 **Design and patients**

72 We analyzed data from the Elderly Cancer Patients (ELCAPA) study, a French, prospective,
73 multicenter, open-cohort, with 19 participating geriatric oncology clinics in the Greater Paris
74 urban area (France). Inclusion criteria were the following: a) patients aged ≥ 70 years, b) with a
75 newly diagnosed solid or hematological cancer, c) having been referred for a multidimensional
76 geriatric assessment (GA) for deciding on a cancer treatment or a change in treatment, and d)
77 with given oral non-opposition from patient or a legally mandated person. The exclusion

78 criteria was the oral opposition of the patient. The primary objective of this survey was to
79 assess the role of GA for decision-making process in older patients with cancer (21). The
80 secondary objective is to identify geriatric and oncologic factors associated with overall
81 survival. The ELCAPA cohort started to include patients in January 2007. Informed consent
82 was obtained from all patients before inclusion. The study protocol was approved by the
83 appropriate institutional review board (*CPP Ile-de-France I*, Paris, France). The survey is
84 registered at ClinicalTrials.gov [NCT02884375]. For the present analysis, we studied patients
85 recruited between January 2007 and March 2016 at 10 participating centers and for whom
86 follow-up and BMI data were available.

87

88 **Data collection**

89 Baseline data was collected prospectively, and included demographic characteristics (age and
90 sex), clinical characteristics (Eastern Cooperative Oncology Group performance status; cancer
91 location and stage), and the results of the GA performed by a senior geriatrician with in-depth
92 expertise in oncology. Functional status was measured by the Activities of Daily Living (ADL)
93 score (22) and the Instrumental ADL (IADL) (23); a patient needing complete assistance in one
94 or more ADL/IADL was considered to be functionally impaired. Mobility was assessed with
95 the timed “up-and-go” (TUG) test, and was considered to be impaired when the completion
96 time was 20 seconds or more (24). Inability to perform the TUG test was also documented.
97 With regard to nutritional status, serum albumin levels and WL in the previous 6 months were
98 recorded. The following prediagnosis WL categories were considered: <5% (minimal), 5-
99 <10% (moderate), and $\geq 10\%$ (severe). Weight and height were measured, in order to calculate
100 the BMI (kg/m^2). We created baseline BMI categories according to the WHO classification and
101 previous studies (25-28), as follows: underweight = BMI <22.5, normal weight = BMI 22.5–
102 24.9, overweight = BMI 25–29.9 and obesity = BMI ≥ 30 . Indeed, for older adults, the French

103 High Commission for Health has suggested a cut-off of $<21 \text{ kg/m}^2$ for malnutrition (rather than
104 $<18.5 \text{ kg/m}^2$) (29), and a recent consensus on malnutrition criteria proposed a cut-point of <22
105 kg/m^2 for low BMI in older people aged >70 years (28). It has recently been suggested that a
106 normal-weight BMI range of 22.5-24.9 could be used for more appropriate comparisons as it is
107 more representative of normal body composition, and shows the lowest mortality (25, 27).
108 Furthermore, a recent study of patients with colorectal cancer showed that a higher BMI cut-off
109 for the reference category may better correspond to adequate muscle mass and adiposity (30).
110 The Mini Nutritional Assessment (MNA) was performed; a score <17 out of 30 corresponded
111 to poor nutritional status (31). Cognitive status was assessed by administering the Mini Mental
112 State Examination (MMSE); a score <24 out of 30 is suggestive of cognitive impairment (32).
113 Mood was assessed using the mini-Geriatric Depression Scale (mini-GDS); a score ≥ 1 out of 4
114 suggests a depressive disorder (33). For each patient, comorbidities were recorded and the
115 Cumulative Illness Rating Scale for Geriatrics (CIRS-G) was used to assess their severity (34).
116 The cancer treatment chosen after the GA was recorded (treatment modalities: surgery,
117 chemotherapy, radiotherapy, hormone therapy, targeted therapy or exclusively supportive
118 care). Inflammation was assessed with regard to the C-reactive protein (CRP) level; a cut-off of
119 $\geq 10 \text{ mg/l}$ was considered to be elevated (35). Metabolically healthy obesity was defined as
120 having less than two of the following cardiometabolic abnormalities: high blood pressure,
121 dyslipidemia, diabetes, and systemic inflammation (36). Lastly, vital status was identified
122 using medical charts, at the public records office, or via the French national vital records
123 register (*Répertoire national d'identification des personnes physiques*). Endpoints were overall
124 12- and 60-months survival, defined as the time from evaluation to death within 12 and 60
125 months or to the last follow-up for censored patients.

126

127 **Statistical analysis**

128 We performed classification and regression tree analyses with recursive partitioning of the
129 overall survival data (37), to further examine the optimal thresholds for the reference category.
130 Using summary statistics, we described the patients' characteristics by BMI category and
131 separately for males and females. Differences between categories were assessed in pairwise
132 comparisons using the Kruskal–Wallis test for quantitative variables and the chi-square or
133 Fischer's exact test for qualitative variables, as appropriate, with Šídák correction for multiple
134 comparisons. Cuzick's non-parametric test was used to assess trend of variables across BMI
135 categories (if responses systematically increase or decrease over the categories of BMI).
136 Univariate and multivariate Cox proportional hazards analyses were conducted after 12 and 60
137 months of follow-up. Clinical and demographic data and known prognostic factors for
138 mortality were studied (38, 39). Interaction terms were tested using the Wald test, and potential
139 confounding factors were investigated, i.e. age, in/out patient status, functional status,
140 comorbidities, smoking status, weight loss, cancer site, metastases, cognitive status, mood,
141 mobility and inflammation. We tested the interaction term between tumor site and metastatic
142 status, in light of a previously reported finding from our ELCAPA cohort (38). Associations
143 with mortality were evaluated by sex and by metastatic status. We further performed survival
144 analysis in the main cancer locations by sex: colorectal, prostate and urinary tract in men;
145 colorectal and breast in women. Because of the low number of women in the pancreas
146 subgroup, we analyzed women with breast and pancreas cancer together, as high BMI in both
147 types of cancer has been associated with worse survival (5, 40). Additional analyses were
148 performed after adjusting for mobility (the TUG result) and inflammation (CRP ≥ 10 mg/L).
149 The proportional-hazards assumption was tested by using Schoenfeld residuals and the
150 Grambsch-Therneau test. The threshold for statistical significance was set to $p < 0.05$. All tests
151 were two-tailed, and all statistical analyses were performed with Stata software (version 15,
152 StataCorp, USA).

153

154 **Results**

155

156 **Study population**

157 Of the 2443 patients recruited into the ELCAPA cohort between January 2007 and March

158 2016, 2071 had a full set of BMI and follow-up data at the time of our analysis (**Figure 1**).

159 When compared with the population not included in the analysis (n=372), the population

160 analyzed had a significantly higher proportion of male patients (52% vs. 38%; $p<0.001$), and

161 thus a higher proportion of patients with prostate cancer (11% vs. 5%; $p=0.001$) and a lower

162 proportion of patients with breast cancer (16% vs. 21%; $p=0.024$). Relative to the non-included

163 patients, the included patients were younger (mean age: 80.7 ± 5.7 vs. 82.7 ± 5.7 ; $p<0.001$),

164 had better cognitive status (75% vs. 63%; $p<0.001$) and were less likely to be underweight

165 (31% vs. 41%; $p=0.03$).

166

167 **Recursive partitioning analysis**

168 After categorizing the continuous BMI into classes of increasing risk in a recursive partitioning

169 analysis, we found that patients with a BMI <22.5 had the highest risk of mortality; this was in

170 line with the cut-off we had defined a priori for our analyses according to the literature.

171

172 **Baseline characteristics**

173 The characteristics of the overall study population and for each BMI category are summarized

174 by sex in **Table 1**. Overall, the median age at inclusion was 81 (interquartile range [IQR]: 77,

175 85); 48% of the patients were women, and 49% had metastases. The tumors were more

176 frequently located in colorectal (17.8%) and breast (16.2%) sites. There were 631 (30%)

177 underweight patients, 466 (23%) patients with a normal weight, 681 (33%) overweight
178 patients, and 293 (14%) obese patients.

179

180 *Pairwise comparisons with regards to the normal BMI category*

181 Compared with male patients in the normal BMI category, overweight male patients were
182 younger ($p=0.022$), less likely to have lost a substantial amount of weight in the previous six
183 months ($p=0.013$), and less likely to have received supportive care ($p=0.028$). Obese male
184 patients were younger ($p=0.001$), less likely to have lost a substantial amount of weight in the
185 previous six months ($p=0.001$) and less likely to have pancreas cancer than male patients in the
186 normal BMI category ($p=0.022$) (**Table 1**).

187 There were no significant differences between overweight female patients and those in the
188 normal BMI category. Compared with female patients in the normal BMI category, obese
189 female patients were younger ($p=0.003$), less likely to be hospitalized at baseline ($p=0.009$),
190 less likely to be current smokers ($p=0.046$), less likely to have lost 10% or more of their body
191 weight in the previous six months ($p<0.001$), and more likely to have an impaired TUG test
192 (>20 s; $p=0.047$) (**Table 1**).

193 The proportion of patients with poor physical performance (impaired or unfeasible TUG test)
194 and median CRP levels decreased gradually as the BMI (in categories) increased in men (p -
195 values for trend <0.0001 for both variables) but not in women (p -values for trend = 0.470 and
196 0.869, respectively).

197

198 **Survival analyses**

199 The median follow-up time was 60 months (range: 0.1–143). The 12- and 60-month overall
200 survival rates were 56.1% [95% confidence interval (CI): 53.9%, 58.2%] and 23.0% [21.1%,
201 25%], respectively. At 12 months, 520 (48.3%) and 383 (38.5%) deaths were observed among

202 the males and females, respectively. At 60 months, these numbers were 844 (78.4%) and 679
203 (68.3%), respectively.

204
205 In the univariate analysis, most variables were significantly associated with 12- and 60-month
206 overall survival in men and women (**Tables 2 and 3**). We found a statistically significant
207 interaction between tumor site and metastatic status ($p < 0.0001$): the adverse effect of having
208 metastases differed across tumor sites. To take into account this modifier effect, we created a
209 composite variable including tumor site and metastatic status. We also detected an interaction
210 between baseline BMI and WL in the six months preceding the cancer diagnosis ($p = 0.043$),
211 and therefore created a variable combining the two. In view of the low number of obese
212 patients with WL 5- <10% (18 males and 25 females) and $WL \geq 10\%$ (12 males and 9 females),
213 we pooled overweight and obese patients of these categories. The interaction between sex and
214 BMI was also statistically significant ($p = 0.048$). As the proportional hazard assumption was
215 not satisfied for the variables “in/out patient status” and “performance status”, these two
216 variables were treated as time-dependent covariates.

217
218 In the multivariate analysis that took account of WL in the six months preceding cancer
219 diagnosis, obese women with $WL < 5\%$ had a lower risk of mortality than normal-weight
220 women with $WL < 5\%$ after 60 months of follow-up only (adjusted hazard ratio [aHR]=0.56;
221 95%CI: 0.37, 0.86); this was after adjustment for age, smoking status, inpatient status,
222 supportive care, performance status, severe comorbidities, and the composite variable
223 combining the cancer site and metastatic status (**Figure 2**). Overweight or obese women with
224 $WL \geq 5\%$ did not have a lower risk of mortality compared with normal-weight women.
225 Overweight and obese men did not have a lower risk of mortality, irrespective of WL. On the
226 contrary, underweight, overweight and obese men with $WL \geq 10\%$ had a higher mortality risk

227 than normal-weight men with WL <5%, at 12- and 60-months of follow-up. Overweight and
228 obese men with WL 5- <10% had also a higher 12-month mortality risk.

229

230 *Mortality according to metastatic status*

231 After stratification by metastatic status, we found similar results in women with metastases but
232 did not observe associations in women without metastases. When compared with normal-
233 weight women with metastases and WL<5%, the aHR [95% CI] for overweight and obese
234 women with metastases and WL<5% was respectively 0.62 [0.39, 1.00] (p=0.049) and 0.58
235 [0.34, 1.00] (p=0.049). For overweight/obese women with WL 5- <10%, the aHR [95% CI] was
236 0.58 [0.33, 0.99] (p=0.048) when compared with normal weight women.

237

238 *Mortality according to cancer site*

239 When we analyzed associations between BMI and mortality by main cancer sites, results were
240 similar as those found in the whole population; overweight and obese women with WL<5%
241 with colorectal or breast cancer showed a better 60-month survival compared to women with
242 normal weight (**Table 4**). In the subgroup of women with breast or pancreas cancer, obese
243 women with WL<5% were at lower mortality risk than normal weight women. Overweight and
244 obese men did not have a lower mortality risk irrespective of cancer site.

245

246 *Sensitivity analysis*

247 Compared with normal-weight women with minimal WL, the additional adjustment for
248 mobility and inflammation (n=423) yielded the following results after 12 and 60 months of
249 follow-up, respectively: aHR=0.84 (95% CI: 0.44, 1.60; p=0.594) and 0.80 (0.52, 1.24; p=0.32)
250 for overweight women with WL<5% ; aHR=0.53 (95% CI 0.25, 1.10; p=0.86) and 0.40 (0.24,
251 0.68; p=0.001) for obese women with WL<5%; aHR=0.85 (0.41, 1.77; p=0.669) and 0.72
252 (0.43, 1.20; p=0.205) for overweight/obese women with WL 5- <10%.

253 For women with metastases, the aHRs [95%CI] for 60-month mortality, after adjustment for
254 mobility and inflammation, were the following: 0.65 [0.37, 1.14] (p=0.13), for overweight
255 women with WL<5%; 0.39 [0.19, 0.79] (p=0.009), for obese women with WL<5%; and 0.56
256 [0.27, 1.15] (p=0.113), for overweight/obese women with WL 5- <10%. No associations with
257 mortality were found in women without metastases.

258

259 **Discussion**

260 In a large population of older patients with various cancer sites and stages, we revealed sex
261 differences in (i) the association between high BMI and mortality and (ii) the effect of WL.

262 After adjustment for confounders and other independent prognostic factors, obese women who
263 had lost <5% of their body weight in the six months preceding cancer diagnosis had lower 60-
264 month mortality risk, relative to normal-weight women with minimal WL. These associations
265 persisted after adjustments for mobility and inflammation. The obesity paradox was not
266 apparent in overweight and obese men.

267 Our results suggest that obesity protected against mortality in older women with cancer with
268 minimal weight loss. This survival advantage has already been shown in studies of various
269 cancers (mainly renal cell carcinoma, colorectal and lung cancer (11, 30, 41)) - suggesting that
270 the increased fat stores and lean body mass in these patients (30, 42) may provide nutritional
271 reserves that counter the effects of the disease. Furthermore, obese individuals constitute an
272 heterogeneous group within which health status, metabolic profiles and functional ability vary
273 markedly from one individual to another (43). Between 20 and 30% of obese adults are thought
274 to be “metabolically healthy”, i.e. with low inflammation and obese-related metabolic
275 complications, few physical disabilities, and low cardiovascular risk (36, 43). In an analysis of
276 the 1999-2004 National Health and Nutrition Examination Survey (NHANES) (36), 29.2% of
277 the obese men and 35.4% of the obese women were metabolically healthy. In the study of Liu

278 et al. (44) this values were respectively, 17.1% and 25.1%, in line with our results. It has been
279 reported that metabolically healthy obese individuals are more likely to have lower waist
280 circumference (36) and less visceral adipose tissue (45), as in the gynoid obesity phenotype. In
281 contrast, metabolically unhealthy individuals are more likely to have greater visceral adiposity.
282 In the present study, we observed a survival advantage for obese women but not for obese men.
283 Sex differences in body composition may explain why the obesity paradox was observed only
284 in women. Indeed, there are marked sex differences in fat distribution: men having greater
285 visceral adiposity and women having greater subcutaneous adiposity. In a study of patients
286 with mostly stage IV cancers (mean age: 64.7 ± 11.3 ; males: 59.4%), low subcutaneous
287 adipose tissue index was an independent predictor of increased mortality (aHR: 1.26; 95% CI:
288 1.11, 1.43; $P < 0.001$) (46); in this study, 25% of women and 49% of men had low subcutaneous
289 adiposity. Furthermore, average blood leptin concentrations are higher in women than in men
290 and higher in overweight and obese individuals than in normal-weight individuals - mainly due
291 to larger subcutaneous fat depots (47). Leptin is reportedly an independent prognostic factor for
292 mortality in some cancers (48, 49). In the NHANES III study, an inverse association between
293 leptin and cancer-related mortality was found in women only (50). The researchers suggested
294 that these contrasting associations may indicate sex-specific biological or environmental
295 pathways linking obesity and cancer in men and women.

296 Our findings were more prominent in women with metastases and WL $< 10\%$, and were in line
297 with a previous study by our research group of older patients with various cancers (mean age:
298 81.2 ± 6.0 ; females: 51%; metastatic cancer: 44.3%); compared with normal weight (BMI 21–
299 24.9), obesity was independently and negatively associated with 6-month mortality in patients
300 with metastatic cancer only (aHR=0.17; 95% CI: 0.03, 0.92; $p=0.04$) (51). It is well known that
301 metastatic cancer is strongly associated with cachexia, loss of skeletal muscle and loss of
302 adipose tissue, due to the greater energy demands of metastatic cells. Sarcopenia has been

303 linked to worse survival in many studies of patients with various solid tumors (52). Accelerated
304 fat loss has been associated with shorter survival in patients with advanced cancer,
305 independently of body weight (53). In this regard, the greater energy stores in adipose tissue in
306 overweight and obese patients with metastatic cancer might protect them against the energy
307 exhaustion induced by the cachectic state and thus give them a survival advantage.

308 In the subgroup analysis by main cancer sites, results were similar as those in the whole
309 population, finding an obesity paradox only in the subgroup of overweight and obese women
310 with WL<5% with colorectal or breast cancers, who showed a lower mortality risk than
311 normal-weight women with WL<5%. Obese women with breast or pancreas cancer also
312 showed a lower mortality risk. Very few studies have analyzed the association between high
313 BMI and survival by sex and by cancer site, and results are somewhat inconsistent. In a pooled
314 analysis of 22 clinical trials (n=11,724 cancer patients with systemic therapy), no associations
315 between BMI and cancer survival among breast and colorectal cancer patients were observed
316 (13); this is different from other studies that have reported an inverse association between BMI
317 and survival in breast (5) and colorectal cancer patients (54). Disparities may depend on the
318 time of BMI assessment. Pre-diagnostic obesity correlates with poor survival in colorectal
319 cancer patients. Conversely, post-diagnostic overweight appears to confer a survival benefit
320 (54). In pancreatic cancer patients, premorbid obesity was associated with increased mortality
321 (40, 55), whereas obesity at diagnosis was not (55). Our findings should be interpreted with
322 caution due to the small numbers of patients in each subgroup.

323 Our study of the prognostic value of a high BMI in a cohort of older patients with various types
324 of cancer has several strengths. Firstly, our analysis took account of potential confounders, and
325 applied an appropriate BMI cut-off for the reference category in order to make more
326 appropriate comparisons. Secondly, we considered WL prior to diagnosis. Indeed, patients in
327 the normal baseline BMI category might have lost substantial weight because of their disease

328 and might therefore have had a higher risk of mortality. In our cohort, 41% of the patients with
329 a normal BMI at the time of the evaluation had lost 5% or more of their body weight in the
330 previous six months, and more than half of the latter patients displayed severe WL (10% or
331 more). In contrast, 69% of overweight and obese patients had not lost weight in the previous
332 six months, and only 8% experienced severe WL.

333 A limitation of the present study is the small sample size and small number of events in some
334 groups, which might have led to a lack of power for the detection of statistically significant
335 associations. The inclusion of older patients with cancer referred by physicians for a geriatric
336 assessment may have also introduced selection bias. The general applicability of our results
337 must also be viewed with caution because of the heterogeneity of our cohort, including patients
338 with various tumor sites and stages. However, analyses were stratified by metastatic status and
339 we performed some subgroup analyses by main cancer sites. We couldn't measure directly
340 adipose and muscle mass. The direct measurement by computerized tomography scan may
341 provide additional information on the role of each, fat and muscle, regarding survival. Finally,
342 although we acknowledge that taking into account the nature of anticancer treatment received
343 by the patient is important, as some treatments may impact body size, we were not able to
344 adjust for this variable because this information was not available. Nevertheless, we adjusted
345 for treatment decision supportive care versus curative/palliative cancer treatment.

346 **Future directions**

347 Our study highlights the importance of (i) using an appropriate BMI cut-off for the reference
348 category in older patients with cancer and (ii) taking account of prediagnosis WL when
349 examining the relationship between obesity and mortality in patients with cancer. Other
350 indicators of adiposity (such as waist circumference and the waist-to-hip ratio) may be more
351 appropriate than BMI. Repeated measures over time would be also useful for investigating
352 changes in weight and lifetime adiposity and their relationships with mortality.

353

354 **Conclusion**

355 Our results evidenced sex differences in the association between high BMI and mortality. By
356 taking account of prediagnosis WL, we observed the obesity paradox solely in a subgroup of
357 older female patients with cancer and WL <5%. Older obese women with WL <5% had a
358 lower mortality risk than normal-weight women with minimal WL. This association was not
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Table 1. Main patient characteristics according to baseline BMI in men and women (N=2071)

	Total ¹ N=2071	Gender	Body mass index (kg/m ²)				p-value ²
			<22.5 Underweight N=631	22.5 - <25 Normal N=466	25 - <30 Overweight N=681	≥30 Obese N=293	
Age at inclusion , median [IQR]	81 [77-85]	M	80 [77-85]	81 [78-85]	80 [76-84] ³	79 [75-83] ^{4,5}	<0.001
		F	83 [79-87]	82 [78-86]	81 [78-86] ⁶	80 [77-84] ^{4,5}	<0.001
Hospitalization at inclusion	677 (32.7)	M	136 (44.9) ⁷	82 (31.8)	110 (28.7) ⁶	30 (22.6) ⁴	<0.001
		F	122 (37.2)	73 (35.1)	92 (30.9)	32 (20.0) ^{4,5}	0.001
Weight loss within the previous 6 months (%) , missing data=235							
<5	1054 (57.4)	M	78 (29.8) ⁷	124 (53.5)	235 (66.6) ^{3,6}	91 (75.2) ^{4,5}	<0.001
5- <10	401 (21.8)		80 (30.5)	55 (23.7)	72 (20.4) ⁶	18 (14.9) ⁴	
≥10	381 (20.8)		104 (39.7) ⁷	53 (22.8)	46 (13.0) ⁶	12 (9.9) ^{4,5}	
<5		F	120 (44.4) ⁷	119 (65.0)	176 (65.2) ⁶	111 (76.6) ⁴	<0.001
5- <10			72 (26.7) ⁷	25 (13.7)	54 (20.0)	25 (17.2)	
≥10			78 (28.9)	39 (21.3)	40 (14.8) ⁶	9 (6.2) ^{4,5}	
Metastases , missing data=249	899 (49.3)	M	183 (68.8) ⁷	110 (51.4)	155 (48.6) ⁶	51 (45.9) ⁴	<0.001
		F	141 (50.0)	81 (48.2)	125 (50.6)	53 (41.7)	0.44
Cancer type , missing data=7							
Colorectal	368 (17.8)	M	62 (20.5)	38 (14.7)	64 (16.8)	24 (18)	0.027
Esophageal/stomach	144 (7.0)		34 (11.2)	24 (9.3)	27 (7.1)	10 (7.5)	
Liver / biliary tract	106 (5.1)		16 (5.3)	18 (7)	22 (5.8)	9 (6.8)	
Pancreas	137 (6.6)		18 (5.9)	20 (7.8)	15 (3.9)	1 (0.8) ⁵	
Prostate	226 (11.0)		48 (15.8)	49 (19)	91 (23.8) ⁶	38 (28.6) ⁴	
Kidney	79 (3.8)		19 (6.3)	11 (4.3)	13 (3.4)	5 (3.8)	
Bladder / urinary tract	225 (10.9)		35 (11.6)	43 (16.7)	68 (17.8)	25 (18.8)	
Hematological malignancies	124 (6.0)		16 (5.3)	14 (5.4)	25 (6.5)	6 (4.5)	
Other ⁹	321 (15.6)		55 (18.2)	41 (15.9)	57 (14.9)	15 (11.3)	

Colorectal		F	64 (19.6)	34 (16.4)	63 (21.3)	19 (12)	0.30
Esophageal/stomach			21 (6.4)	11 (5.3)	11 (3.7)	6 (3.8)	
Liver / biliary tract			16 (4.9)	7 (3.4)	13 (4.4)	5 (3.2)	
Pancreas			28 (8.6)	16 (7.7)	31 (10.5)	8 (5.1)	
Kidney			10 (3.1)	7 (3.4)	10 (3.4)	4 (2.5)	
Bladder / urinary tract			18 (5.5)	11 (5.3)	16 (5.4)	9 (5.7)	
Breast	334 (16.2)		96 (29.4)	75 (36.2)	84 (28.4)	74 (46.8) ^{4,8}	
Hematological malignancies			21 (6.4)	14 (6.8)	20 (6.8)	8 (5.1)	
Other ¹⁰			53 (16.2)	32 (15.5)	48 (16.2)	25 (15.8)	
Comorbidities (CIRS-G grade 3-4)							
median [IQR]	1 [0-2]	M	1 [0-2] ⁷	1 [0-2]	1 [0-2] ⁶	1 [0-2] ⁴	<0.001
≥1 comorbidity CIRS-G grade 3-4	1120 (54.1)		202 (66.7) ⁷	148 (57.4)	199 (52.0) ⁶	67 (50.4) ⁴	<0.001
median [IQR]		F	1 [0-2] ⁷	0 [0-1]	0 [0-1] ⁶	0 [0-1] ⁴	0.009
≥1 comorbidity CIRS-G grade 3-4			194 (59.1) ⁷	95 (45.7)	141 (47.3) ⁶	74 (46.2) ⁴	0.003
Poor ECOG PS (≥2), missing data=8							
	1061 (51.4)	M	203 (67.4) ⁷	126 (49)	151 (39.5) ⁶	55 (41.4) ⁴	<0.001
		F	190 (58.3)	103 (49.5)	145 (49)	88 (55)	0.078
Impaired ADL (≤5), missing data=29							
	637 (31.2)	M	126 (42.4)	81 (31.5)	90 (23.9)	27 (20.6)	<0.001
		F	118 (36.2)	62 (30.7)	85 (28.9)	48 (30.4)	0.23
Smoking status, missing data=270							
Never smokers	968 (53.8)	M	90 (33.6)	69 (29.7)	111 (34.2)	35 (30.4)	0.23
Former smokers	708 (39.3)		146 (54.5)	146 (62.9)	189 (58.2)	73 (63.5)	
Current smokers	125 (6.9)		32 (11.9)	17 (7.3)	25 (7.7)	7 (6.1)	
Never smokers		F	223 (76.9)	145 (80.1)	191 (75.8)	104 (75.4)	0.013
Former smokers			52 (17.9)	27 (14.9)	41 (16.3)	34 (24.6)	
Current smokers			15 (5.2)	9 (5)	20 (7.9)	0 (0) ^{4,5,8}	
Timed "up-and-go" test, missing data=299							
<20 sec.	1081 (61.0)	M	144 (55.4)	147 (64.2)	227 (68.8) ⁶	81 (72.3) ⁴	<0.001
≥20 sec.	436 (24.6)		59 (22.7)	56 (24.5)	65 (19.7)	24 (21.4)	
Unable to perform the test	255 (14.4)		57 (21.9) ⁷	26 (11.4)	38 (11.5) ⁶	7 (6.3) ⁴	
<20 sec.		F	157 (55.9)	108 (63.2)	148 (56.9)	69 (53.5)	0.069

≥20 sec.			73 (26.0)	35 (20.5)	80 (30.8)	44 (34.1) ⁵	
Unable to perform the test			51 (18.1)	28 (16.4)	32 (12.3)	16 (12.4)	
CRP , median [IQR]; missing data=605	12.8 [3-48]	M	22 [7-66]	15 [3-61]	11 [3-39] ⁶	7 [3-20]	0.011
		F	12.1 [2.5-48]	11.5 [3-38]	11.2 [2.9-40]	8.9 [3.5-34]	0.81
Supportive care , missing data=275	369 (20.5)	M	93 (35.4) ⁷	54 (23.0)	45 (13.8) ^{3,6}	17 (14.4) ⁴	<0.001
		F	66 (23.1)	32 (18.1)	43 (16.6)	19 (14.5)	0.12

¹ Values in this column correspond to those of the total population

² p-value: Kruskal–Wallis test for quantitative variables and chi-square or Fischer's exact test for qualitative variables, as appropriate.

³ Significant pairwise comparisons between overweight and normal patients

⁴ Significant pairwise comparisons between obese and underweight patients

⁵ Significant pairwise comparisons between obese and normal patients

⁶ Significant pairwise comparisons between overweight and underweight patients

⁷ Significant pairwise comparisons between underweight and normal patients

⁸ Significant pairwise comparisons between obese and overweight patients

⁹ Lung (N=60), skin (N=35), unknown primary origin (N=26), head and neck (N=10), brain (N=9), sarcoma (N=8), breast (N=5), thyroid (N=4), other (N=11).

¹⁰ Gynecologic (N=49), lung (N=25), skin (N=22), unknown primary origin (N=19), sarcoma (N=16), brain (N=6), head and neck (N=4), thyroid (N=3), other (N=14).

Abbreviations: ADL, activities of daily living; BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; F, female; IQR, interquartile range; M, male.

Table 2. Univariate analysis of 12-month survival (N=2071) by sex

Feature	Males (n=1077)		Females (n=994)	
	HR [95% CI]	p-value ¹	HR [95% CI]	p-value ¹
Age at inclusion (years)	1.03 [1.01, 1.04]	0.001	1.02 [1.01, 1.04]	0.004
Hospitalization at inclusion	2.80 [2.35, 3.32]	<0.0001	2.59 [2.11, 3.16]	<0.0001
Living alone at home	1.22 [1.00, 1.48]	0.051	1.02 [0.83, 1.25]	0.85
Baseline BMI (kg/m ²)				
Underweight: <22.5	1.64 [1.31, 2.07]	<0.0001	1.65 [1.25, 2.18]	<0.0001
Normal: 22.5-24.9	1(reference)		1(reference)	
Overweight: 25-29.9	0.88 [0.69, 1.11]		1.03 [0.76, 1.40]	
Obese: ≥30	0.70 [0.50, 0.98]		0.72 [0.49, 1.06]	
Weight loss in the previous six months				
<5%	1(reference)	<0.0001	1(reference)	<0.0001
5- <10%	2.13 [1.70, 2.67]		1.85 [1.40, 2.43]	
≥10%	3.14 [2.52, 3.90]		3.13 [2.42, 4.04]	
Tumor site and metastatic status				
Colorectal M0	1(reference)	<0.0001	1(reference)	<0.0001
Colorectal M1/Mx	2.37 [1.38, 4.06]		3.25 [1.80, 5.87]	
Upper digestive tract/liver/pancreas M0	2.11 [1.20, 3.69]		2.98 [1.62, 5.48]	
Upper digestive tract/liver/pancreas M1/Mx	5.40 [3.27, 8.92]		9.20 [5.24, 16.1]	
Breast or prostate M0	0.19 [0.07, 0.52]		0.36 [0.17, 0.77]	
Breast M1/Mx	4.85 [1.43, 16.4]		2.31 [1.29, 4.15]	
Prostate M1/Mx	2.57 [1.53, 4.30]		—	
Other urologic malignancies M0	1.71 [0.99, 2.95]		1.94 [0.94, 4.03]	
Other urologic malignancies M1/Mx	3.77 [2.25, 6.33]		4.96 [2.56, 9.63]	

Hematologic malignancies	2.28 [1.27, 4.11]		2.44 [1.29, 4.61]	
Other malignancies M0	3.13 [1.72, 5.68]		1.80 [0.88, 3.68]	
Other malignancies M1/Mx	5.47 [3.30, 9.05]		3.71 [2.09, 6.62]	
CRP \geq 10 mg/L	2.77 [2.21, 3.46]	<0.0001	3.15 [2.41, 4.11]	<0.0001
Supportive care	3.00 [2.48, 3.64]	<0.0001	3.76 [3.00, 4.71]	<0.0001
Previous cancer treatment	0.99 [0.79, 1.24]	0.92	0.79 [0.59, 1.08]	0.14
ECOG-PS				
0-1	1(reference)	<0.0001	1(reference)	<0.0001
2	1.99 [1.57, 2.54]		1.91 [1.42, 2.56]	
\geq 3	4.58 [3.75, 5.60]		4.45 [3.5, 5.67]	
Smoking status				
Never smoker	1(reference)	0.43	1(reference)	0.73
Former smoker	1.10 [0.90, 1.35]		1.10 [0.83, 1.45]	
Current smoker	1.24 [0.88, 1.75]		0.91 [0.54, 1.53]	
Number of severe comorbidities (CIRS-G grade 3-4)	1.34 [1.26, 1.42]	<0.0001	1.33 [1.24, 1.42]	<0.0001
Number of daily drugs prescribed	1.06 [1.04, 1.09]	<0.0001	1.07 [1.04, 1.10]	<0.0001
ADL, score \leq 5	2.84 [2.38, 3.38]	<0.0001	2.98 [2.43, 3.65]	<0.0001
IADL, score $<$ 8	2.03 [1.63, 2.53]	<0.0001	2.96 [2.27, 3.85]	<0.0001
Timed "up-and-go" test				
$<$ 20 sec.	1(reference)	<0.0001	1(reference)	<0.0001
\geq 20 sec.	2.30 [1.84, 2.87]		2.20 [1.70, 2.85]	
Unable to perform the test	5.07 [4.00, 6.43]		4.29 [3.25, 5.65]	
MMSE score $<$ 24	1.37 [1.09, 1.74]	0.008	1.84 [1.45, 2.34]	<0.0001
mini-GDS score \geq 1	1.91 [1.58, 2.30]	<0.0001	1.63 [1.31, 2.01]	<0.0001

¹ Logrank test for categorical variables and Wald test for quantitative variables

Abbreviations: ADL, activities of daily living; BMI, body mass index; CI, confidence interval; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IADL, instrumental activities of daily living; mini-GDS, mini-Geriatric Depression Scale; MMSE, Mini Mental State Examination.

Table 3. Univariate analysis of 60-month survival (N=2071) by sex

Features	Males (n=1077)		Females (n=994)	
	HR [95% CI]	p-value	HR [95% CI]	p-value ¹
Age at inclusion (years)	1.03 [1.02, 1.05]	<0.0001	1.03 [1.02, 1.05]	<0.0001
Hospitalization at inclusion	2.31 [2.01, 2.66]	<0.0001	2.02 [1.73, 2.36]	<0.0001
Living alone at home	1.24 [1.06, 1.44]	0.008	0.98 [0.84, 1.14]	0.81
Baseline BMI (kg/m ²)				
Underweight: <22.5	1.51 [1.25, 1.81]	<0.0001	1.31 [1.07, 1.61]	<0.0001
Normal: 22.5-24.9	1(ref)		1(ref)	
Overweight: 25-29.9	0.84 [0.70, 1.01]		0.95 [0.77, 1.18]	
Obese: ≥30	0.74 [0.58, 0.95]		0.60 [0.46, 0.79]	
Weight loss in the previous six months				
<5%	1(ref)	<0.0001	1(ref)	<0.0001
5- <10%	1.87 [1.57, 2.23]		1.74 [1.43, 2.13]	
≥10%	2.56 [2.15, 3.06]		2.57 [2.10, 3.15]	
Tumor site and metastatic status				
Colorectal M0	1(ref)	<0.0001	1(ref)	<0.0001
Colorectal M1/Mx	2.46 [1.71, 3.53]		2.46 [1.69, 3.58]	
Upper digestive tract/liver/pancreas M0	1.81 [1.23, 2.67]		2.26 [1.52, 3.37]	
Upper digestive tract/liver/pancreas M1/Mx	4.15 [2.91, 5.92]		7.28 [5.0, 10.61]	
Breast or prostate M0	0.37 [0.23, 0.59]		0.42 [0.28, 0.64]	
Breast M1/Mx	3.54 [1.27, 9.83]		2.13 [1.49, 3.04]	
Prostate M1/Mx	2.48 [1.75, 3.53]		—	
Other urologic malignancies M0	1.45 [1.01, 2.10]		1.84 [1.17, 2.90]	

Other urologic malignancies M1/Mx	3.07 [2.14, 4.42]		4.06 [2.58, 6.41]	
Hematologic malignancies	1.79 [1.19, 2.70]		1.57 [1.03, 2.38]	
Other malignancies M0	2.51 [1.62, 3.87]		1.53 [0.96, 2.44]	
Other malignancies M1/Mx	4.48 [3.14, 6.40]		2.93 [2.03, 4.24]	
CRP \geq 10 mg/L	2.45 [2.07, 2.90]	<0.0001	2.29 [1.90, 2.75]	<0.0001
Supportive care	2.59 [2.19, 3.05]	<0.0001	2.92 [2.42, 3.53]	<0.0001
Previous cancer treatment	1.09 [0.91, 1.29]	0.35	0.90 [0.72, 1.12]	0.36
ECOG PS				
0-1	1(ref)	<0.0001	1(ref)	<0.0001
2	1.75 [1.47, 2.09]		1.80 [1.47, 2.20]	
\geq 3	3.36 [2.87, 3.93]		3.15 [2.65, 3.75]	
Smoking status				
Never smokers	1(ref)	0.58	1(ref)	0.99
Former smokers	1.08 [0.92, 1.26]		1.02 [0.82, 1.25]	
Current smokers	1.12 [0.85, 1.48]		0.99 [0.69, 1.44]	
Number of severe comorbidities (CIRS-G grade 3-4)	1.31 [1.25, 1.38]	<0.0001	1.33 [1.26, 1.40]	<0.0001
Number of daily drugs prescribed	1.05 [1.03, 1.08]	<0.0001	1.05 [1.03, 1.07]	<0.0001
ADL, score \leq 5	2.26 [1.96, 2.61]	<0.0001	2.35 [2.01, 2.74]	<0.0001
IADL, score $<$ 8	1.73 [1.48, 2.03]	<0.0001	2.36 [1.97, 2.82]	<0.0001
Timed "up-and-go" test				
$<$ 20 sec.	1(ref)	<0.0001	1(ref)	<0.0001
\geq 20 sec.	1.93 [1.62, 2.31]		1.75 [1.45, 2.12]	
Unable to perform the test	3.91 [3.19, 4.81]		3.03 [2.43, 3.78]	
MMSE score $<$ 24	1.26 [1.05, 1.52]	0.014	1.51 [1.26, 1.82]	<0.0001
mini-GDS score \geq 1	1.73 [1.49, 2.02]	<0.0001	1.42 [1.20, 1.66]	<0.0001

¹ Logrank test for categorical variables and Wald test for quantitative variables

Abbreviations: ADL, activities of daily living; BMI, body mass index; CI, confidence interval; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IADL, instrumental activities of daily living; mini-GDS, mini-Geriatric Depression Scale; MMSE, Mini Mental State Examination.

Table 4. Multivariate analysis of 12 and 60-month survival according to the main cancer locations by sex

Outcome	Men						Women					
	Cancer site	Deaths (%)	BMI category, WL	aHR ^{1,2}	95% CI	p-value	Cancer site	Deaths (%)	BMI category, WL	aHR ^{1,2}	95% CI	p-value
12-months survival	Colorectal (n=135)	48 (36)	OW, <5%	1.74	0.50, 6.01	0.38	Colorectal (n=115)	40 (35)	OW, <5%	0.08	0.02, 0.39	0.002
			Obese, <5%	1.94	0.42, 8.94	0.40			Obese, <5%	0.08	0.01, 0.80	0.031
			OW/Obese, 5-<10%	1.36	0.34, 5.41	0.66			OW/Obese, 5-<10%	0.07	0.01, 0.37	0.002
	Prostate (n=148)	40 (27)	OW, <5%	2.43	0.62, 9.58	0.20	Breast (n=197)	33 (17)	OW, <5%	1.17	0.33, 4.17	0.81
			Obese, <5%	3.01	0.57, 15.9	0.19			Obese, <5%	0.75	0.21, 2.65	0.65
			OW/Obese, 5-<10%	13.61	2.93, 63.2	0.001			OW/Obese, 5-<10%	0.98	0.16, 6.07	0.99
	Urinary tract (n=144)	75 (52)	OW, <5%	3.07	0.94, 9.97	0.062	Breast / Pancreas (n=253)	76 (30)	OW, <5%	1.69	0.66, 4.30	0.28
			Obese, <5%	2.60	0.76, 8.85	0.13			Obese, <5%	0.81	0.29, 2.26	0.68
			OW/Obese, 5-<10%	5.74	1.44, 22.9	0.013			OW/Obese, 5-<10%	1.83	0.65, 5.12	0.25
60-months survival	Colorectal (n=135)	97 (72)	OW, <5%	0.82	0.35, 1.91	0.64	Colorectal (n=115)	84 (73)	OW, <5%	0.34	0.13, 0.87	0.025
			Obese, <5%	1.41	0.50, 3.99	0.51			Obese, <5%	0.30	0.09, 1.01	0.053
			OW/Obese, 5-<10%	0.97	0.40, 2.32	0.94			OW/Obese, 5-<10%	0.43	0.17, 1.11	0.082
	Prostate (n=148)	90 (61)	OW, <5%	1.27	0.61, 2.66	0.52	Breast (n=197)	86 (44)	OW, <5%	0.46	0.22, 0.94	0.033
			Obese, <5%	0.91	0.36, 2.30	0.85			Obese, <5%	0.43	0.20, 0.92	0.030
			OW/Obese, 5-<10%	4.09	1.61, 10.4	0.003			OW/Obese, 5-<10%	0.55	0.15, 1.99	0.36
	Urinary tract (n=144)	116 (81)	OW, <5%	1.34	0.67, 2.68	0.42	Breast / Pancreas (n=253)	139 (55)	OW, <5%	0.72	0.39, 1.31	0.28
			Obese, <5%	1.15	0.53, 2.51	0.72			Obese, <5%	0.50	0.25, 0.99	0.045
			OW/Obese, 5-<10%	1.90	0.76, 4.74	0.17			OW/Obese, 5-<10%	1.08	0.51, 2.26	0.85

¹ adjusted Hazard ratios for age, smoking status, metastatic status, supportive care and the number of severe comorbidities. Inpatient status and Eastern Cooperative Oncology Group performance status were treated as time-dependent covariates.

² Reference category: Normal BMI, <5% of weight loss

Abbreviations: BMI, body mass index; CI, confidence interval; OW, overweight; WL, weight loss.

Figure captions:

Figure 1. Study flow chart

Figure 2. Adjusted Hazard Ratios of overall 12- (**A, B**) and 60-months (**C, D**) mortality according to BMI and weight loss, for men (**A, C**; n=721) and women (**B, D**; n=633).

Legend

Abbreviations: BMI, body mass index; **N**, normal (BMI: 22.5-24.9); **OW**, overweight (BMI: 25-29.9); **O**, obese (BMI: ≥ 30); **UW**, malnourished/underweight (BMI: < 22.5).

The hazard ratios were adjusted for age, smoking status, inpatient status, cancer site in association with metastatic status, supportive care, Eastern Cooperative Oncology Group performance status, and the number of severe comorbidities (grade 3-4 according to the Cumulative Illness Rating Scale for Geriatrics). Inpatient status and Eastern Cooperative Oncology Group performance status (ECOG-PS) were treated as time-dependent covariates.